REMARKS

Reconsideration and withdrawal of the rejections of the application are requested in view of the amendments and remarks presented herein, which place the application into condition for allowance.

I. Status Of Claims And Formal Matters

Claims 69-74, 76-105, 145, 156, 162-181, 193-202 are currently pending in this application. Claims 69-73 have been withdrawn. Claims 126-128, and claims 182-192 have been cancelled herein.

Claim 91 has been amended to eliminate the recitation "rapidly", which is replaced by "the rapid detection of". Claim 145 has been amended to eliminate the recitations "recent or ongoing" and "thereby detecting a recent or ongoing WNV infection". Claims 198-200 have been amended to eliminate the recitation "recent or ongoing". These amendments depict the changes to the claims intended in the June 22, 2006 Amendment. Applicants apologize for the error. Claim 202 has been amended to correct a grammatical error.

No new matter is added by these amendments.

The Examiner is thanked for withdrawing the rejections under 35 U.S.C. §112, first and second paragraphs.

It is submitted that the claims are patentably distinct over the prior art and that these claim are and were in full compliance with the requirements of 35 USC §112. The amendments of the claims herein are not made for the purpose of patentability within the meaning of 35 USC §§ 101, 102, 103 or 112; but rather, the amendments are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the amendments should not give rise to any estoppel, as they are not narrowing amendments.

The Examiner is respectfully requested to consider and make of record U.S. Patent No. 6,766,817, issued to da Silva et al., entitled "Fluid Conduction Utilizing a Reversible Unsaturated Siphon with Tubarc Porosity Action,"; and U.S. Patent Publication No. 2006-0115896, by Wong et al., entitled "Diagnostic Test for West Nile Virus"; and Udeni, B.R. *et al.*, Detection Of Antibodies To West Nile Virus In Equine Sera Suing Microsphere Immunoassay, J. Vet. Diagn. Invest. 18:392-395 (2006) (copy enclosed), which are also cited on the accompanying Supplemental Information Disclosure Statement and PTO-1449.

Any reference made herein to the present application is with respect to Paragraph Nos. of the published version of this application, namely US Publication No. 2004/0197769, which published October 7, 2004.

II. Priority

The Examiner has alleged that the current pending claims are not entitled to benefit of the priority date of October 31, 2002 of provisional application 60/422,755. The Office Action asserts that the present application claims a method of detecting WNV infection by testing for NS5 protein, and that the NS5 protein is not disclosed in 60/422,755.

Applicants maintain the position that the priority date of the present claims should be October 31, 2002, not June 6, 2003. NS5 is mentioned on page 4 of the specification of provisional application 60/422,755. Furthermore, there are a number of instances throughout the specification wherein viral proteins are referred to, clearly including NS5. For example, on page 24, the specification states, "In another embodiment of this invention, the WNV polypeptides described herein are prepared as part of a larger fusion protein. For example, a WNV polypeptide used in a composition of this invention may be fused at its N-terminus or C-terminus to a ***different immunogenic WNV polypeptide***, to a non-WNV polypeptide or to combinations thereof, to produce fusion proteins comprising the WNV polypeptide." Furthermore, "polypeptide" as defined on page 18 clearly encompasses NS5.

Accordingly, Applicants submit there is no impediment to allowance of Applicant's original claim for priority. Thus the filing date of **October 31, 2002** is used for the purpose of applying prior art.

III. The Rejections Under 35 U.S.C. §103 Are Overcome

Claims 74, 76-105, 126-128, 145, 156, and 162-202 are rejected under 35 USC §103(a) as allegedly being obvious over Wang et al. ("Wang"), Valdes et al. ("Valdes"), Mandy et al ("Mandy"), Scaramozzino et al ("Scaramozzino"), and McDonell et al ("McDonell").

The Office Action asserts that it would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the teaching of Wang, Valdes and Mandy to use WNV NS5 protein to detect WNV infections in humans and horses. Further, that a person of ordinary skill in the art would have been motivated to use the NS5 and E proteins as immunodiagnostic assays for the detection of WNV in biological samples. And, that McDonell teaches a diagnostic kit with an immunogenic composition using ELISA and fluorescent

labeling. The Office Action further contends that one would have expected success because of the teachings of Scaramoizzino who developed a rapid, sensitive PCR assay for the detection of flavivirus with NS5 gene sequences.

To establish a prima facie case of obviousness, there must be a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. There must also be a reasonable expectation of success. Further still, the prior art reference alone or in combination must teach or suggest all the claim limitations. In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991). Applicants respectfully submit that the claims under rejection are not prima facie obvious over Wang, Valdes, Mandy, Scaramozzino, and McDonell since, inter alia, there lacks any motivation or suggestion to combine the references. Further, it is respectfully submitted that neither the references themselves nor the knowledge of persons of ordinary skill in the art provide any motivation or suggestion to combine the references.

Arguments from our previous response, filed March 17, 2005 remain relevant. Therein, Applicants reviewed the contrast between the present invention and the prior art at the time the instant application was filed. Specifically, Applicants responded to assertions that the claims of the present invention were prima facie obvious over Wang in view of Valdes and further in view of Mandy. In response, the present Office Action asserts that the claimed invention is obvious under 35 U.S.C. §103(a) in view of the combination of Wang, Valdes, Mandy, McDonell, and Scaramoizzino.

A. WANG IS NOT PRIOR ART

Initially, Applicants would like to point out that **Applicants previously submitted, on March 17, 2005, a Declaration pursuant to 37 C.F.R. § 1.132** (hereinafter "Declaration of March 17, 2005 ") stating that Wang is not the work of others as defined by 35 USC §102(a). Applicants re-attach the Declaration for Examiner's convenience. **Applicants respectfully request consideration of this Declaration**. Applicants respectfully assert that the Declaration of March 17, 2005 is sufficient to overcome the grounds of rejection of claims 74, 76-105, 126-128, 145, 156, and 162-202 as obvious Wang, Valdes, Mandy, McDonell, and Scaramoizzino because the Declaration of March 17, 2005 clearly states that T. Wang, L.A. Magnarelli, J.F. Anderson, L.H. Gould, S.L. Bushmich, and E. Fikrig did not make an independent inventive

contribution to the invention claimed in this application. Therefore, it is respectfully submitted that Wang is not prior art.

B. THE INVENTION IS NOT OBVIOUS EVEN IF WANG IS TAKEN INTO CONSIDERATION

Assuming arguendo that Wang could be considered prior art, Applicants assert that it does not make the present invention obvious. Wang relates to a method of detecting a WNV infection in an animal. More in particular, this reference relates to the preparation of and testing of recombinant forms of WNV E, M and NS1 antigens against sera obtained from horses known to be infected with WNV. The reference utilizes immunoblots to assess the performance of each of the antigens in the serodiagnosis of WNV infections. As Applicants previously argued, Wang reports that the WNV E protein is immunodominant and that "[a]ntibodies to the M protein or NS1 protein were not detected by immunoblot in all 10 West Nile virus-infected horses or six humans with West Nile virus." (See page 107 of Wang). Thus, although the WNV E protein detected WNV-infected horse and human sera, neither M or NS1 detected any sera. Given Wang's data that WNV E was "immunodominant" against the tested sera while WNV M nor NS1 were non-reactive, and given that nonstructural proteins (like NS1 or NS5) would generally be regarded by the ordinarily skilled person as less immunogenic than a viral structural protein (like E), Wang would not be suggestive to the skilled artisan that NS5, another nonstructural protein, would likely be a good candidate to detect a WNV infection with specificity and without substantial cross-reactivity to other flaviruses, especially JEV, DENV, and SLEV. Thus, Wang would in fact teach away from the present invention. Thus, the combination of this reference with Valdes, Mandy, Scaramozzino, and McDonell would not be proper.

Valdes relates to a method of characterizing the immune response to ***DENV*** structural and nonstructural proteins. In particular, Valdes tests sera from DENV fever patients and DENV hemorrhagic fever patients against DENV-2 and DENV-4 antigens E, NS1, NS3, and NS5 using Western blotting procedures. Therefore, this references relates to an entirely different virus than the present invention. As Applicants argued previously, in light of Wang which shows that a nonstructural protein is a poor antigen to use to detect WNV-infected sera, and in view of the fact that Valdes relates to an entirely different virus, namely DENV, at best, it would have been "obvious to try" combining the references. The Examiner, however, is reminded that "obvious to try" is not the standard under 35 USC §103. *In re Fine*, 5 USPQ 2d 1596, 1599 (Fed. Cir.

1988). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggest the desirability of the combination. See MPEP 2143.01. It is respectfully submitted that neither Wang nor Valdes provides the requisite suggestion or desirability to be combined to reach each and every element of the invention.

Further, to establish *prima facie* obviousness of a claimed invention, each of the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 (CCPA 1974); also MPEP 2143.03. It is respectfully submitted that neither Wang nor Valdes, either alone or in combination, teaches nor suggests each and every element of claimed invention. For example, neither reference teaches or suggests a method for detecting a WNV infection in a subject by contacting a biological sample with a substantially purified NS5 protein or an immunogenic fragment thereof having a native conformation or non-denatured structure whereby the NS5 protein is specifically reactive with anti-WNV antibodies but not substantially cross reactive with antibodies against JEV, SLEV, or DENV. For example, Wang relates to the use of WNV E protein to detect a WNV infection, whereas the present invention relates, *inter alia*, to the use of WNV NS5 in a method to detect a WNV infection. And, surely Wang does not teach a WNV NS5 that has a native conformation or non-denatured structure and that is specifically cross-reactive with anti-WNV antibodies but not substantially cross reactive with other flaviviruses, especially JEV, SLEV, and DENV.

Valdes relates to analyzing the antibody response to DENV infected sera, including the response to DENV E, NS1, NS3, and NS5 antigens. Contrary to Valdes, the instantly claimed invention relates to detecting WNV infections, not DENV infections. Although DENV and WNV are related flaviviruses, it would not have been obvious to extend the results of Valdes to modify , especially in view of the inconsistent data and lack of data presented in Valdes. For example, the reactivity of NS3 from DENV-2 and DENV-4 is completely different and NS5 is tested for only a single DENV type (see Table 1). Valdes does not correct for the deficiencies in Wang, and vice versa. Neither Wang nor Valdes, either alone or in combination, teach a method for the detection of a WNV infection in a subject suspected of having said infection that includes the step of contacting a biological sample from the subject with an isolated and substantially purified polypeptide comprising a WNV NS5 protein having a native conformation or non-denatured structure whereby the NS5 protein or the immunogenic fragment thereof is specifically

reactive with anti-WNV antibodies but not substantially cross-reactive with antibodies against JEV, SLEV, or DENV.

Moreover, because Valdes relates to DENV, and not WNV, Applicants point out that the differences in the method of transmission between the viruses is relevant. In particular, because humans are amplifying hosts for dengue viruses, the patients have high levels in the blood for long enough time that mosquitoes can transmit the virus to other humans through biting an infected individual. The situation with WNV, however, is different. Humans are not amplifying hosts and the viral load in a human infected with WNV is so low that mosquitoes cannot transmit WNV from one infected human to another. This difference is important, because one skilled in the art would have no motive to postulate that NS5 of WNV would have been a good diagnostic antigen since there was not reason to presuppose that with low viremia, infected humans would have had a strong immune response, i.e., generating antibodies against WNV NS5. Accordingly, the combination of this reference with Wang, Mandy, Scaramozzino, and McDonell would not be proper.

Mandy relates to an immunoassay that makes use of a new technology, suspension array technology (SAT). SAT involves using flow cytometry to make quantitative measurements, using microfluorospheres as solid support (coated with protein) and antibodies as reporter molecules. The reference is concerned with describing critical aspects and limitations of SAT. Contrary to the contention in the Office Action that "Mandy teaches that antibodies that are used in ELISA assays can predictably be used in SAT assays", this reference notes that SAT use as an immunoassay was, at the time of publication, essentially still in a developmental stage, including commercial availability of kits (page 714, 720, and 723); that "the impact of multiplexed assays has been limited to date" (page 720); that the "...implementation of SAT for biomedical research is *anticipated*" (page 720); and that cytokine panels are representative of immunoassays that are most likely to gain wide application and possible acceptance, for monitoring drug and vaccine trials against various infectious agents (page 720). Furthermore, Mandy only generically refers to SAT, such as multiplex assays on Luminex. Although it discusses *potential*, it fails to demonstrate that SAT is an effective diagnostic tool for any flavivirus infection, and certainly not for WNV in particular. On the contrary, the present invention demonstrated the use of SAT in differentiating WNV infection from either infection or vaccination with other flaviviruses.

Accordingly, the combination of this reference with Wang, Valdes, Scaramozzino, and McDonell would not be proper.

Scaramozzino relates to the design of new primers allowing heminested PCR involving the alignment of NS5 gene sequences of 30 different flaviviruses. The reference relates to a ***genus*** PCR procedure that might serve as a first-line diagnostic PCR screening test for an unknown virus. The procedure would not ensure a definitive phylogenetic analysis. Although this initial procedure may take only a few hours, a definitive identification to the pathogenic members of the genus Flavivirus would require *further* complete sequencing or cell culture.

Moreover, Scaramozzino is a molecular amplification test, which is only capable of detecting and measuring a virus if it is still present in the host. On the other hand, while the present invention is able to detect a current infection, it is also useful as a diagnostic for *prior* infection of a flavivirus. Scaramozzino provided no incentive or motivation to use NS5 as an antigen for antibody protection. In particular, Scaramozzino did not teach or suggest that NS5 would be a successful antigen for antibody detection. In essence, the use of a sequence in a PCR procedure cannot be said to predict the effectiveness of the structural protein derived from that sequence in an immunological procedure. Accordingly, the combination of this reference with Wang, Valdes, Mandy, and McDonell would not be proper.

McDonell involves a recombinant ***NS1***/E composition, although the reference suggests that other NS proteins may replace NS1. The reference discusses the potential usefulness of the composition as a vaccine and in immunoassays. However, McDonell only relates to NS1 and DENV infections. Although DENV and WNV are related flaviviruses, it would not have been obvious to extend the results of McDonell to arrive at the present invention, especially in view of the unpredictability of immune responses to antigenic proteins from different viruses. Accordingly, the combination of this reference with Wang, Valdes, Mandy, and Scaramozzino would not be proper.

Neither Wang, Valdes, Mandy, Scaramozzino, nor McDonell either alone or in combination, teach a method for the detection of a WNV infection in a subject suspected of having said infection that includes the step of contacting a biological sample from the subject with an isolated and substantially purified polypeptide comprising a WNV NS5 protein having a native conformation or non-denatured structure whereby the NS5 protein or the immunogenic

fragment thereof is specifically reactive with anti-WNV antibodies but not substantially cross-reactive with antibodies against JEV, SLEV, or DENV.

C. THE INVENTION IS NOT OBVIOUS IN VIEW OF THE DECLARATION SUBMITTED HEREWITH

Applicants further request reconsideration and withdrawal of the 35 U.S.C. §103 rejection in view of Wang, Valdes, Mandy, Scaramozzino, and McDonell in view of the Declaration pursuant to 37 C.F.R. § 1.132 submitted herewith (hereinafter "Declaration of February 2007"). The Declaration of February 2007 declares and states that the at the time of filing of the present application, the state of the art did not teach or suggest to one of skill in the art that recombinant NS5 could be used with the Luminex platform to arrive at the present invention.

Accordingly, in view of the preceding comments, reconsideration and withdrawal of the 35 USC §103 rejection in view of Wang, Valdes, Mandy, Scaramozzino, nor McDonell is respectfully requested.

V. Double Patenting Is Held In Abeyance

The Office Action provisionally rejects claims 74-105, 126-128, 145 and 156, and 162-202 under judicially created doctrine of double patenting over claims 1-9, 13-21, 24-35 and 56-57 of copending Application No. 10/839,442.

The issue of whether there is indeed double patenting is contingent upon whether the remarks herewith are indeed considered and entered; and, if so, whether the Examiner believes there is overlap with claims ultimately allowed in the application.

Accordingly, reconsideration and withdrawal of the double patenting rejection, or at least holding it in abeyance until agreement is reached as to allowable subject matter, is respectfully requested.

REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, an interview with the Examiner is respectfully requested, prior to issuance of any paper other than a Notice of Allowance; and, the Examiner is respectfully requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application, reconsideration and withdrawal of the rejections of and objections to the application, and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date.

Respectfully submitted,

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